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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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PETERS VERNY JONES & SCHMITT, L.L.P.
425 SHERMAN AVENUE
SUITE 230
PALO ALTO, CA 94306

EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 05/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/928,227	MAHAN ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6,9,11-18,24,28-32 and 47-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,9,11-18,24,28-32 and 47-51* is/are rejected.

7)☐ Claim(s) *1,3,6,9,11-18 and 51* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.O

DETAILED ACTION

Claims 2,4,5,7,8,10,19-23,25-27,33-46 have been canceled.
Claims 1,3,6,9,11-18,24,28-32,47-51 are pending; all claims have been amended or through dependence upon an amended claim.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections/Rejections Maintained

2. Claims 11,16-18 objected to for depending upon a rejected base claim is maintained in light of the claims not having been amended into independent form and still depend from a rejected base claim.

Objections/Rejections Withdrawn

3. Claims 1 and 5 are no longer objected to; claim 5 has been canceled and claim 1 has been amended to recite the term "tetranucleotide".

4. Claims 1,3,6,9,12-13,47-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Torreblanca et al(1996), in light of a new combination of claim limitations set forth in all of these claims and Applicant's remarks.

5. Claims 1,12-13 Claims 24,29-31 rejected under 35 USC 102(e) as anticipated by Kleanthous et al (US Pat. 6,585,975, as evidenced by Torreblanca et al(1996) .

6. Claims 3,6, 28,32, 48-50 rejected under 35 USC 103(a) as obvious over the combination of Kleanthous et al (US Pat. 6,585,975, in view of Torreblanca et al(1996), in light of a new combination of claim limitations set forth in all of these claims, and Applicant's remarks.

1. Claims 1,3,6,9,12,14-15,47 and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Bandyopadhyay et al (1994), in light of new combination of claim limitations and new grounds of rejection set forth below.

Response to Arguments

2. Applicant's arguments with respect to claims February 14, 2005have been considered but are moot in view of the new ground(s) of rejection.

New Combinations of claim limitations have been submitted:

Independent claim 1 has been amended from a method that provided a composition with the second step of contacting to a four-step method; claim 1 now recites steps of growing, contacting, separating and adding.

Independent claim 24 has been amended to recite the phrase "vaccine composition" instead of just the term "composition".

Independent claim 48 has been amended to recite the phrase "vaccine composition" instead of just the term "composition".

New claim 51 has been submitted as a four-step method similar to claim 1.

New Claim Limitations/New Grounds of Rejection

Claim Objections

3. Claims 1, 3,6,9,11-18, 47,49, 51, 48 and 50 are objected to because of the following informalities:

4. Amended claims 1, 3,6,9,11-18, 47,49 , and new claim 51 recite the phrase " separating the bacteria from said culture medium and excess agent and adding to **it** a pharmaceutically acceptable excipient"; what is "it"? The "it" recited in the claims can refer to the bacteria, the culture medium or the excess agent . The recitation of the term "it" should be amended to recite a specific noun to clearly define what is added to the excipient.

5. Claims 48 and 50 recite semi-colons";" between the members of the recited Markush group; the Markush group should recite commas "," between the members of the group. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. Claims 24, 28-31, 32, 48 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

7. Claims 24, 28-31, 32, 48 and 50 have been amended to administer a vaccine composition that is defined by the claims to be a bacteria that has an alteration in the native dam gene for the treatment of pathogenic bacterial infection in a subject that is already infected, the subject populations including mammals and humans.

8. The instant amended method claims are directed to treating an infected subject but do not require, nor structurally define the administered compositions to produce or comprise any specific infection associated virulence factors/antigens for the pathogenic bacteria causing infection. The infection that already exists in the subject produces specific substances that result in infection and the composition administered to the subject does not comprise any specific substances, antigens, or structural characteristics that would specifically treat the infection in the subject.

9. No common antigens or molecular relationship is required for the administered attenuated bacteria relative to the pathogenic bacteria causing infection. The attenuation of the bacteria does not require the administered bacteria to evidence any infection specific inhibitory activity. Inhibition of proliferation of an existing bacterial infection through administration of a non-related attenuated pathogenic bacteria that evidences a mutation in the dam gene would not induce nor provide any type of treatment nor protection against that already existing infection. Klemm et al (2000, abstract, International Journal of Medical Microbiology) teach that bacterial pathogens have specific adhesions for host tissue cells, and also teach a critical relationship between host specificity and tissue tropism for infections to be established. Klemm et al teach

that different pathogenic bacteria produce different adhesion characteristics that effect infection. Klemm et al also states that a large number of bacterial adhesins with individual receptor specificities have been identified, and are prone to rapid microevolution which results in changes in the receptor specificity of individual adhesins. Klemm et al address the fact that one bacterium would not serve to competitively displace another bacteria because all bacteria do not produce the same adhesion molecules associated with infection. Nieman et al (2004, Microbes and Infection) states that pathogenic bacteria produce a "rich diversity of adhesive and invasive strategies" which "pose a multitude of seemingly unrelated problems to cell biologists and medical professionals". Both Klemm et al and Nieman et al address the fact that a single attenuated bacterium would not serve to treat a subject that is already infected with a pathogenic bacteria that produces virulence factors that the attenuated bacterium can not or is unable to combat because of attenuation or because the attenuated bacteria does not produce the same or equivalent virulence factors associated with the pathogenic bacteria causing the subject's infection that would in turn serve to treat the existing infection.

10. The prior art teaches vaccines to not predictably produce the desired protection against pathogenic bacterial infections. De Berardinis et al (2004, Future Drugs Ltd.) states that "immune responses elicited in clinical trials have been disappointingly low (page 673, col. 1)". Alsahii et al (2001, Digestive Diseases) teaches a whole cell H.pylori composition could possibly induce harmful autoimmune antibodies that cross-react with human cells (see page 153, col. 1, paragraph 2) that share the same surface antigens that H.pylori produces. Alsahii et al (2001) also teach that there are still "[A] variety of questions regarding H.pylori management in general can also be pertinent to vaccine therapy. (see page 154, col. 2, paragraph 1)."

11. All bacteria do not cause infection in the same location. The attenuated bacteria composition is not administered to the site of the pathogenic bacterial infection, and the attenuated bacterium is not required to migrate to or to co-locate in area of the subject which is already infected. The instant claims administer the composition by any route, and is not required to be a route that would result in treatment of infection.

12. The instant Specification does not provide enabling disclosure, guidance, and teaching on how any bacteria that evidences an alteration in the dam methylase activity, albeit an increase or decrease, can be used to treat any type of preexisting infection, in any infected subject, for any pathogenic bacteria that has already established infection, when the composition is administered by any route, especially when the attenuated bacteria does not evidence any specific structures or molecules that would serve as pathogenic bacteria infection inhibitors.

13. The newly amended claims are not enabled for treating pre-existing infection caused by a pathogenic bacteria in any subject through administering the vaccine composition now claimed, because while the person of skill in the art could make the recited composition, But they could not use the composition for treating a subject because a single vaccine composition would not serve to provide protection against the hundreds of different pathogenic bacteria for the reasons set forth above. The claimed subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

14. Amended claims 1,3,6,9, 11-18 , 47,49 and new claim 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Amended claims 1,3,6,9, 11-18 , 47,49 and new claim 51 recite the limitation "excess agent" in reference to an agent that prevents the bacteria's dam gene expression, but the agent is

not added in the contacting step in an excess amount, therefore the term "excess amount" lacks antecedent basis in the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

15. Claim 1 and 9, 12-13, 47 and 49 are rejected under 35 U.S.C. 102(e) as being anticipated by Ritchie et al (1986, reference submitted by Applicant in the USPTO 1449, dated May 13, 2002) as evidenced by US Pat. 6120774.

16. Ritchie et al disclose the instantly claimed method of making a composition having reduced bacterial virulence of a pathogenic bacteria, the method comprising the steps of:

Growing (see page 420, col. 1, S. typhimurium NR5038) in culture medium (see page 420, col. 1, paragraph 2 "log-phase cells") a virulent bacteria having a DNA methyltransferase (see title, Salmonella typhimurium, and page 429, col. 1, paragraph 1, first sentence 5'-GATC-3') activity ;

Contacting the bacteria with an agent (see page 420, col. 1, paragraph 2 "0.1 M sodium citrate buffer (pH 5.6) with N-methyl-N-nitro-N'-nitrosoguanidine (50 ug/ml)) that prevents the bacteria's dam gene expression (see "deficient in DNA adenine methylation, title) which alters the native level of methylation of adenine (see NR5265, and LT2 were altered in methylation, and LT2 was deficient (see title);

Separating the bacteria from said culture medium and excess agent (see page 420, col. 1, paragraph 2 "after 30 min at 37 degrees C. After removal of the mutagen by centrifugation, cells were plated on nutrient yeast agar) and **adding** to it a pharmaceutically acceptable excipient

(nutrient yeast agar, yeast extract, NaCl and agar (as evidence by US Pat. 6120774 that shows in claim 21 that a culture or agar stab is a type of pharmaceutically acceptable excipient for a vaccine).

Instant claim 9: the mutagen bound to DNA and caused the loss of expression of Dam methylase activity (see Figure 1).

Instant claims 12-13: wherein the agent altered the native Dam gene of Salmonella typhimurium.

Instant claim 47-49: two additional agents were used to introduce additional mutations, specifically a polynucleotide in the form of a mutH101::Tn5 mutation introduced by a P22 bacteriophage transduction which inserted a kanamycin resistance gene and introduction of a plasmid containing a coding sequence for a functional dam gene of E.coli (see page 420, col. 2, paragraph 1). The reference inherently anticipates the instantly claimed invention as now claimed.

1. Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

2. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

Please Note: No specific structure(s) is required for the recited "agent" in claim 1 or any of the dependent claims, and the "agent" must only cause a change in the phenotypic functional

characteristics of the virulent bacteria through the recitation of the phrase "altering the bacteria's native level of methylation of adenine" and "reducing virulence of the bacteria" . The following art rejections are being made of record in light of Applicant's combination of functional phenotypic characteristics newly required by the amended claims

17. Claims 1 and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Thune et al (US Pat. 6,010,705, reference submitted by Applicant in the USPTO 1449, dated May 13, 2002).

Thune et al disclose the instantly claimed method of making a composition having reduced bacterial virulence of a pathogenic bacteria, the method comprising the steps of:

Growing (see col. 8, line 7 "cultures") in culture medium(see col. 6, "standard microbiological methods and API 20e test strips") a virulent(see abstract, "Live-attenuated vaccines, incapable of reversion to virulence") bacterial (see col. 5, line 62 "Isolation of wild type") having a DNA methyltransferase (see col. 18, lines 6-8 defines the bacteria as having a methyltransferase activity specific for adenine (see col. 18, line 4 "adenine") activity ;

Contacting the bacteria (E. ictaluri purA gene was amplified from genomic E.ictaluri DNA using PCR primers derived from conserved regions of E.coli purA gene, col. 8, lines 50-53) with an agent (see col. 10, lines 28-49 "conjugation was conducted with E.coli"; see col. 9, lines 64-67 "to facilitate mutagenesis of the E.ictaluri purA gene" and also see col. 18, lines 59-67 "mutations include point mutations within the gene or promoter (insertion, deletion or alteration); insertion of a transposon, mini-transposon or other sequence into the gene or promoter (see col. 19, lines 1-7) which alters the native level (reduced levels of adenine, produces and alters native levels of methylation due to reduced cites for methylation) of methylation of adenine (starved for adenine, col. 18, lines 3-4), thereby reducing the virulence

(attenuated) of the bacteria (see col. 18, lines 3-4 "the attenuated E. ictaluri is starved for adenine", which results in an altered native level methylation of adenine, and reduced virulence);

Separating the bacteria from said culture medium and excess agent (see col. 10, lines 39-40 "Bacteria were collected on a Gelman TM 0.45 um Metricel filter" and see col. 11, lines 6-8 "pelleted by centrifugation) and **adding** to it a pharmaceutically acceptable excipient (pellets were resuspended in 0.9 ml of sterile 0.9% saline, and added to a fish "food product comprising said vaccine", see col. 20, claim 12) .

Instant claim 47: wherein the agent is a polynucleotide (primer from E.coli, and plasmid (see paragraphs immediately above) . The reference anticipates the instantly claimed invention as now claimed.

Conclusion

18. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

19. WO92/11361 is cited to show attenuated Salmonella strains with phoP mutations.

20. US Patents 6,190,669 (Figure 2) ; 6,399,074; 6680182; Curtiss US Pat. 5,855,880 are cited to show attenuated Salmonella strains and/ or recombinantly expressed proteins.

21. Posfai et al (1984) is cited to show DNA methyltransferase for Bacillus subtilis (abstract).

22. Labbe et al (1990) is cited to show Neisseria DNA methyltransferase (abstract).

23. Demidova, GV et al (1984) is cited to show Yersinia pestis DNA-methylase (abstract).

24. Lyngstadaas et al (1999) is cited to show E.coli dam gene to be in an operon with aroB (abstract only).

25. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
May 9, 2005

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600